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Ecofriendly and efficient multicomponent method for preparation of 1-amidoalkyl-2-naphthols using maltose under solvent-free conditions

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Abstract An efficient and entirely green protocol for preparation of 1-amidoalkyl-2-naphthols employing a multicomponent one-pot condensation reaction of 2-naphthol, amides or urea, and aromatic aldehydes in the presence of maltose under solvent-free conditions is described. The present approach of this methodology offers several advantages such as mild conditions, high yields, clean reaction profiles, operational simplicity, and environmentally benign and simple work-up procedures.

Keywords Green protocol · Amidoalkyl naphthols · Multicomponent reaction · Maltose · Solvent-free conditions

Introduction

Multicomponent reactions (MCRs) play an important role in combinatorial chemistry because of their ability to synthesize small drug-like molecules with several degrees of structural diversity. These reactions allow compounds to be synthesized in few steps and usually in a one-pot manner [1]. As well as offering time and energy savings and having simple procedures, the advantages of these reactions include high bond-forming efficiency and low expenditure [2]. Therefore, finding and designing new MCRs has been the subject of extensive research.

Amidoalkyl naphthols and their derivatives have attracted considerable interest in recent years in terms of biologically important antibacterial properties, natural products, and potent drugs, including a number of nucleoside antibiotics and human immunodeficiency virus (HIV) protease inhibitors, such as ritonavir and lopinavir [3, 4]. 1-Amidomethyl-2-naphthols can be converted into important "drug-like"

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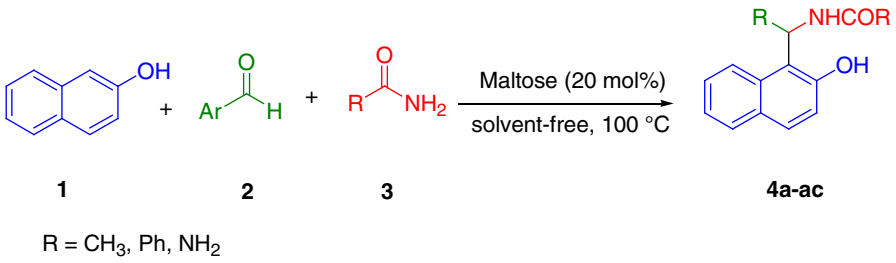
1-aminomethyl-2-naphthols by amide hydrolysis [5]. The hypertensive and bradycardiac effects of these compounds have been evaluated [6]. Intramolecular cyclization of amidoalkyl naphthols by Vilsmeier reagent produces 1,3-oxazines [7]. Synthesis of 1,3-oxazines has attracted attention because of their potential as antibiotics [8] and as antitumor [9], anticonvulsant [10], antipsychotic [11], antimalarial [12], antianginal [13], and antihypertensive [14] agents, and as potent antirheumatic agents [15]. Preparation of 1-amidoalkyl-2-naphthols can be carried out by condensation of aryl aldehydes, 2-naphthol, and acetonitrile or acetamide in the presence of Lewis or Brønsted acid catalysts such as montmorillonite K_{10} clay [16], $Ce(SO_4)_2$ [17], iodine [18], succinic acid [19], $Fe(HSO_4)_3$ [20], ethylammonium nitrate (EAN) [21], TrCl [22], and zeolite H-BETA [23]. However, the major problems associated with these reactions in most of the published procedures are high catalyst loading, long reaction times, unsatisfactory yields, harsh reaction conditions, expensive catalysts, and tedious work-up procedures. Therefore, development of a suitable method using additional reagents and catalysts for efficient synthesis of 1-amidoalkyl-2-naphthols remains an attractive field for researchers.

In view of the above and as a part of our ongoing program on MCRs [24, 25], we present herein an ecofriendly, simple, and efficient method for synthesis of 1-amidoalkyl-2-naphthol compounds via a one-pot three-component reaction using 2-naphthol, amides/urea, and aromatic aldehydes in the presence of maltose under solvent-free conditions (Scheme 1).

The principles of green chemistry have been introduced to eliminate or reduce the use of hazardous materials such as H_2SO_4 or H_3PO_4 in chemical processes. Cleaner technologies are possible using environmentally friendly materials such as carbohydrates, because these materials are cheap, safe, and environmentally benign [26]. For this reason, we focused our investigation on the development of new green synthetic methods for preparation of 1-amidoalkyl-2-naphthols. This is a one-pot reaction under solvent-free conditions, which is not only operationally simple, clean, and efficient but also consistently gives the corresponding products in good to excellent yields.

Results and discussion

We performed a set of preliminary experiments on 2-naphthol, acetamide, and benzaldehyde in the presence of catalyst as a model reaction. In the initial work,



Scheme 1 Maltose-catalyzed synthesis of 1-amidoalkyl-2-naphthols **4**

different carbohydrates as catalyst were screened in the model reaction. The reaction did not progress even after 24 h in the absence of catalyst. Also, the reaction was performed in the presence of sucrose, xylose, and lactose, with the product being obtained in moderate yield. However, 20 mol.% maltose proved to be an efficient catalyst, giving high yield (Table 1). As shown in Table 1, the shortest time and best yield were achieved at 100 °C.

To evaluate the generality of the process, several examples illustrating the present method for synthesis of 1-amidoalkyl-2-naphthols **4** were studied (Table 2). The reactions of 2-naphthol with various aromatic aldehydes and amides or urea were carried out in the presence of 20 mol.% maltose at 100 °C. In all the reactions, good to excellent yields were obtained in short reaction times (0.2–2 h). Clean and complete conversions leading to the corresponding amidoalkyl naphthols were observed, and no side products such as dibenzoxanthenes were formed. Aromatic aldehydes carrying either electron-withdrawing (nitro) or electron-donating (halide, alkyl, alkoxy) groups were all suitable for the reaction. On the other hand, the scope of different amide components was studied. Both amides (benzamide and acetamide) and urea participated well in the reactions. As compared with the amides, urea afforded the corresponding amidoalkyl naphthol in longer reaction time (Table 2).

A suggested mechanism for this transformation is proposed in Scheme 2. As reported in the literature [27], reaction of 2-naphthol with aldehydes in the presence of catalyst is known to give *ortho*-quinone methides (*o*-QMs). The same *o*-QMs, generated in situ, have been reacted with amides via conjugate addition to form 1-amidoalkyl-2-naphthol derivatives **4a**–**ac**.

Conclusions

We have developed a new method for preparation of 1-amidoalkyl-2-naphthol derivatives via one-pot three-component reaction of 2-naphthol with aromatic

Table 1 Optimization of catalyst for synthesis of 1-amidoalkyl-2-naphthols

Entry	Catalyst	Mol.%	Temperature (°C)	Time (h)	Yield (%)[a]
1	Lactose	10	100	8	48
2	Sucrose	10	100	5	65
3	Xylose	10	100	7	25
4	Maltose	10	100	5	80
5	Maltose	15	100	4	85
6	**Maltose**	**20**	100	**2**	**93**
7	Maltose	30	100	1	87
8	Maltose	20	80	5	72
9	Maltose	20	120	2	75

Reaction conditions: 2-naphthol, acetamide, and benzaldehyde in the presence of catalyst

The best result were obtained with 20 mol.% maltose in 100 °C are highlighted in bold

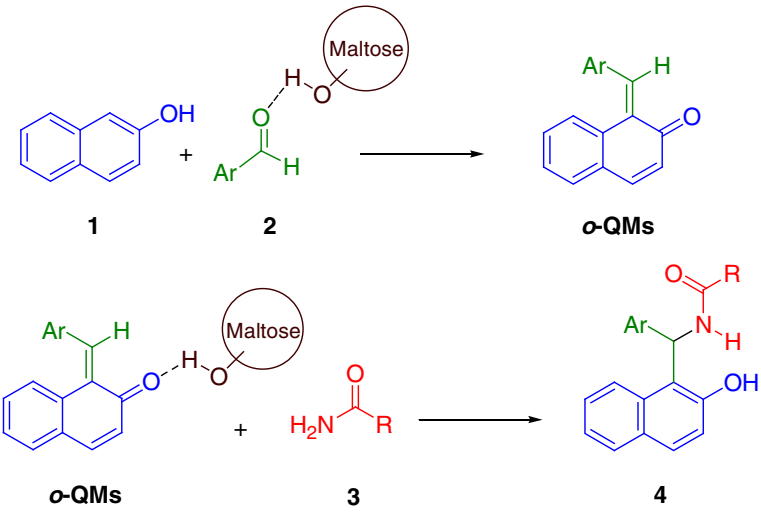
[a] Isolated yield

Table 2 Synthesis of 1-amidoalkyl-2-naphthol derivatives

Entry	Ar	R	Time (h)	Yield (%)[a]	Product	M.p. (lit. m.p.) (°C)
1	4-NO_2–C_6H_4	CH_3	0.5	94	**4a**	246–248 (248–250) [6]
2	4-Cl–C_6H_4	CH_3	0.5	92	**4b**	228–229 (230–232) [20]
3	3-NO_2–C_6H_4	CH_3	0.5	91	**4c**	238–240 (236–237) [29]
4	2,4-$Cl_2C_6H_3$	CH_3	0.5	94	**4d**	199–201 (201–203) [6]
5	3-OMe–C_6H_4	CH_3	1	89	**4e**	203–205 (203–205) [29]
6	2-Me–C_6H_4	CH_3	1.5	80	**4f**	197–199 (200–202) [34]
7	4-Me–C_6H_4	CH_3	1.5	87	**4g**	221–223 (223–225) [28]
8	Ph	CH_3	1	90	**4h**	243–245 (245–246) [18]
9	2-Cl–C_6H_4	CH_3	0.5	95	**4i**	197–199 (194–196) [29]
10	4-NCC_6H_4	CH_3	0.5	89	**4j**	230–232 (232–234) [18]
11	4-OMe–C_6H_4	CH_3	1	89	**4k**	181–183 (184–186) [18]
12	Ph	Ph	0.5	96	**4l**	242–244 (242–243) [6]
13	2-NO_2–C_6H_4	Ph	0.3	95	**4m**	262–264 (264–266) [33]
14	2,4-$Cl_2C_6H_3$	Ph	0.3	95	**4n**	238–240 (238–239) [30]
15	4-Me–C_6H_4	Ph	1.5	88	**4o**	215–216 (207–209) [18]
16	4-NO_2–C_6H_4	Ph	0.5	92	**4p**	238–240 (237–239) [32]
17	2-Cl–C_6H_4	Ph	0.5	92	**4q**	264–266 (265–267) [30]
18	3-NO_2–C_6H_4	Ph	0.3	90	**4r**	234–236 (237–239) [18]
19	4-Cl–C_6H_4	Ph	1.5	90	**4s**	186–188 (187–189) [29]
20	4-NC–C_6H_4	Ph	0.2	96	**4t**	176–178 (176–178) [35]
21	4-NMe_2–C_6H_4	Ph	0.5	89	**4u**	218–220 (220–221) [33]
22	4-OMe–C_6H_4	Ph	1.5	88	**4v**	208–210 (206–208) [33]
23	3-NO_2–C_6H_4	NH_2	1	90	**4w**	192–194 (192–193) [18]
24	4-NO_2–C_6H_4	NH_2	1	92	**4x**	192–194 (163–165) [17]
25	4-Cl–C_6H_5	NH_2	1.5	90	**4y**	166–168 (168–169) [34]
26	Ph	NH_2	2	85	**4z**	174–176 (174–175) [31]
27	2,3-$(MeO)_2$–C_6H_3	Ph	0.5	95	**4aa**	236–238
28	2-OH,5-Br–C_6H_3	Ph	0.8	92	**4ab**	220–222
29	C_4H_3S	Ph	1	92	**4ac**	221–223

[a] Isolated yield

aldehydes and different amides/urea using maltose as a neutral organic catalyst at 100 °C under solvent-free conditions. The catalyst shows environmentally friendly characters. Namely, it is inexpensive, clean, safe, nontoxic, and easily obtained. Moreover, this method has several other advantages including mild reaction conditions, high yields, operational simplicity, and clean and neutral reaction conditions, which makes it a useful and attractive process for synthesis of a wide variety of biologically active compounds.



Scheme 2 Suggested mechanism for synthesis of amidoalkyl naphthols

Experimental

Melting points and infrared (IR) spectra of all compounds were measured on an Electrothermal 9100 apparatus and a JASCO FT/IR 460 Plus spectrometer, respectively. The ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on Bruker DRX-400 Avance instruments with dimethyl sulfoxide (DMSO) as solvent. Mass spectra were recorded on an Agilent Technology (HP) spectrometer operating at ionization potential of 70 eV. All reagents and solvents obtained from Fluka and Merck were used without further purification.

Typical procedure for synthesis of 1-amidoalkyl-2-naphthols (**4a**–**ac**)

Maltose (20 mol.%, 0.068 g) was added into a mixture of benzaldehyde (1 mmol), 2-naphthol (1 mmol), and acetamide (1.1 mmol), then the reaction mixture was heated to 100 °C and maintained for the appropriate time (Table 1). After completion of the reaction as monitored by thin-layer chromatography (TLC), the reaction mixture was washed with H_2O (3 × 10 mL). The catalyst is solvable in water and was removed from the reaction mixture. Then, the residue was recrystallized from EtOH.

*N-[(2,3-Dimethoxyphenyl)-(2-hydroxynaphthalen-1-yl)-methyl]-benzamide (**4aa**)*

Yield: 95 %; m.p. 236–238 °C; IR (KBr, cm^{-1}): 3,379 (N–H), 3,143 (O–H), 1,632 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.56$ and 3.76 (2s, 6H, 2OCH$_3$), 6.92 (dd, 1H, $J = 8$ Hz, $J = 1.6$ Hz, $H_{aromatic}$), 6.96 (t, 1H, $J = 8.4$ Hz, $H_{aromatic}$), 7.12 (d, 1H, $J = 6.8$ Hz, $H_{aromatic}$), 7.20 (d, 1H, $J = 8.8$ Hz, $H_{aromatic}$), 7.28 (t, 1H,

$J = 7.6$ Hz, $H_{aromatic}$), 7.45 (t, 3H, $J = 7.6$ Hz, $H_{aromatic}$), 7.50–7.53 (m, 2H, $H_{aromatic}$), 7.74 (d, 1H, $J = 8.6$ Hz, $H_{aromatic}$), 7.79 (d, 1H, $J = 7.6$ Hz, $H_{aromatic}$), 7.86 (d, 2H, $J = 6.8$ Hz, $H_{aromatic}$), 8.21 (d, 1H, $J = 8.0$ Hz, $1H_{benzylic}$), 8.98 (d, 1H, $J = 8.0$ Hz, NH), 10.20 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d6): $\delta = 45.94$, 56.09, 60.34, 112.14, 119.13, 119.25, 121.00, 122.98, 123.47, 123.83, 126.76, 127.59, 128.74, 128.88, 129.45, 131.72, 132.92, 134.95, 135.78, 146.68, 152.78, 153.70, 165.38; MS *m/z* (%): 413 (M^+, 25), 382 (17), 308 (35), 261 (100), 246 (31), 218 (30), 167 (73), 149 (86), 127 (19), 105 (63), 77 (58), 57 (54).

N-[(4-Bromo-2-hydroxyphenyl)-(2-hydroxynaphthalen-1-yl)-methyl]-benzamide ***(4ab)***

Yield: (92 %); m.p. 220–222 °C; IR (KBr, cm^{-1}): 3,379 (N–H), 3,225 (O–H), 1,599 (C=O); ^1H NMR (400 MHz, DMSO-d_6): $\delta = 6.76$ (d, 1H, $J = 8.4$ Hz, $H_{aromatic}$), 7.20 (d, 1H, $J = 9.2$ Hz, $H_{aromatic}$), 7.22 (d, 1H, $J = 2.8$ Hz, $H_{aromatic}$), 7.28 (t, 1H, $J = 7.2$ Hz, $H_{aromatic}$), 7.39–7.53 (m, 6H, $H_{aromatic}$), 7.74 (d, 1H, $J = 8.8$ Hz, $H_{aromatic}$), 7.79 (d, 1H, $J = 7.6$ Hz, $H_{aromatic}$), 7.86 (d, 2H, $J = 7.8$ Hz, $H_{aromatic}$), 8.24 (d, 1H, $J = 8.8$ Hz, $H_{benzylic}$), 8.94 (brs, 1H, NH), 10.12 (brs, 2H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 45.90$, 110.17, 117.73, 118.63, 119.29, 122.97, 123.53, 126.72, 127.74, 128.69, 128.79, 128.88, 129.53, 130.90, 130.96, 131.70, 132.02, 133.00, 134.83, 153.79, 154.67, 165.66; MS *m/z* (%): 447 (M^+, 5), 311 (45), 261 (7), 247 (16), 202 (5), 144 (81), 121 (6), 105 (100), 77 (89), 51 (35).

N-[(2-Hydroxynaphthalen-1-yl)-thiophen-3-ylmethyl]-benzamide ***(4ac)***

Yield: (92 %); m.p. 221–223 °C; IR (KBr, cm^{-1}): 3,420 (N–H), 3,108 (O–H), 1,630 (C=O); ^1H NMR (400 MHz, DMSO-d_6): $\delta = 7.23$ (d, 1H, $J = 8.8$ Hz, $H_{aromatic}$), 7.29–7.35 (m, 2H, $H_{aromatic}$), 7.43–7.57 (m, 6H, $H_{aromatic}$), 7.75 (d, 2H, $J = 8.4$ Hz, $H_{aromatic}$), 7.81 (d, 1H, J = 9.2 Hz, $H_{aromatic}$), 7.88 (d, 2H, $J = 6.8$ Hz, $H_{aromatic}$), 8.04 (d, 1H, $J = 8.8$ Hz, $H_{benzylic}$), 9.10 (d, 1H, $J = 6.4$ Hz, NH), 10.11 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 49.54$, 109.64, 117.89, 119.01, 119.36, 123.08, 123.22, 126.56, 127.42, 127.80, 127.84, 127.98, 128.83, 128.90, 129.16, 130.34, 132.02,132.60, 133.65, 134.48, 153.88, 166.69; MS *m/z* (%): 378 (M^+, 18), 273 (6), 256 (100), 227 (11), 144 (5), 122 (11), 105 (32), 77 (26), 57 (10).

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